

CLINICAL RESEARCH

CORONARY

Three-Year Outcomes After Revascularization With Everolimus- and Sirolimus-Eluting Stents From the SORT OUT IV Trial

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ABSTRACT

OBJECTIVES The study sought to compare the risk of late outcome with a focus on very late definite stent thrombosis of the everolimus-eluting stent (EES) with that of the sirolimus-eluting stent (SES) at 3-year follow-up.

BACKGROUND In the SORT OUT IV (SORT OUT IV Trial), comparing the EES with the SES in patients with coronary artery disease, the EES was noninferior to the SES at 9 months. The SORT OUT IV trial provides long-term head-to-head randomized comparison of the EES with the SES.

METHODS We prospectively randomized 2,774 patients in the SORT OUT IV trial. Follow-up through 3 years was complete in 2,771 patients (99.9%). The 3-year pre-specified endpoints were composites of safety and efficacy (major adverse cardiac events [MACE]: cardiac death, myocardial infarction, target vessel revascularization, and definite stent thrombosis).

RESULTS At 3 years, the composite endpoint MACE occurred in 9.8% of the EES group and in 11.1% of the SES group (hazard ratio [HR]: 0.89, 95% confidence interval [CI]: 0.70 to 1.12). Overall rate of definite stent thrombosis was lower in the EES group (0.2% vs. 1.4%; HR: 0.15, 95% CI: 0.04 to 0.50), which was largely attributable to a lower risk of very late definite stent thrombosis: 0.1% versus 0.8% (HR: 0.09, 95% CI: 0.01 to 0.70).

CONCLUSIONS At 3-year follow-up, the MACE rate did not differ significantly between EES- and SES-treated patients. A significant reduction of overall and very late definite stent thrombosis was found in the EES group. (The SORT OUT IV TRIAL [SORT OUT IV]; [NCT00552877](https://clinicaltrials.gov/ct2/show/study/NCT00552877)). (J Am Coll Cardiol Intv 2014;7:840-8) © 2014 by the American College of Cardiology Foundation.

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In percutaneous coronary interventions, drug-eluting stent (DES) implantation has reduced the need for repeat revascularization compared with bare metal stents (1-3). Although DES are widely accepted as effective and safe, debate continues on the safety of first-generation DES, given the potential for late stent thrombosis, especially after discontinuation of dual antiplatelet therapy (4,5). Increased risk of late and very late stent thrombosis associated with first-generation drug-eluting stents led to recommendations for large-scale randomized clinical endpoint trials encompassing a variety of patient categories and types of coronary lesions to allow head-to-head comparison of DES with higher external validity than in the pivotal trials performed in more select lesions/patient populations. In the COMPARE (Second-Generation Everolimus-Eluting and Paclitaxel-Eluting Stents in Real-life Practice) trial (6) and the SPIRIT IV (Everolimus-Eluting Versus Paclitaxel-Eluting Stents in Coronary Artery Disease) trial (7), a lower rate of very late definite stent thrombosis in the second-generation everolimus-eluting stent (EES) compared with the first-generation comparator paclitaxel-eluting stent (PES) was found between 1 and 2 years after stent implantation. The favorable stent thrombosis rate for the second-generation DES has awaited confirmation in longer term follow-up randomized studies. In the RESOLUTE (Comparison of Zotarolimus-Eluting and Everolimus-Eluting Coronary Stents) trial (8), the everolimus-eluting stent (EES) was associated with significantly less definite stent thrombosis than the slow-release Resolute (Medtronic, Minneapolis, Minnesota) zotarolimus-eluting stent (ZES). However, in the SORT OUT III (SORT OUT IV Trial) trial, the fast-release Endeavor ZES (Medtronic) was associated with a reduced risk of very late definite stent thrombosis compared with the SES at 3-year follow-up (9) and in the ENDEAVOR IV Clinical Trial: A Trial of a Coronary Stent System in Coronary Artery Lesions, the rate of very late stent thrombosis was significantly lower with ZES compared with PES (10). The SORT OUT IV trial aimed to compare the safety and efficacy outcomes at 3 years with specific focus on very late definite stent thrombosis of the first-generation SES Cypher Select+ (Medtronic) and the second-generation EES Xience V/Promus stent (Medtronic) in a population-based setting, using registry-based event detection.

METHODS

PATIENTS AND STUDY DESIGN. SORT OUT IV (11) is a randomized, multicenter, single-blind, all-comer, 2-arm, noninferiority trial comparing the EES with the

SES in treating atherosclerotic coronary artery lesions. The study period was August 2007 to June 2009. The detailed study protocol can be found in the main publication (12). Briefly, patients were eligible if they were at least 18 years of age, had chronic stable coronary artery disease or acute coronary syndromes, and at least 1 coronary lesion with >50% diameter stenosis, requiring treatment with a DES. If multiple lesions were treated, the allocated study stent had to be used in all lesions. No restrictions were placed on the number of treated lesions, the number of treated vessels, or lesion length. Exclusion criteria were life expectancy of <1 year; an allergy to aspirin, clopidogrel, sirolimus, or everolimus; participation in another randomized trial; or inability to provide written informed consent.

RANDOMIZATION. Patients were enrolled by the investigators and randomly allocated to treatment groups after diagnostic coronary angiography and before percutaneous coronary intervention. Block randomization by center (permuted blocks of random sizes [2/4/6]) was used to assign patients in a 1:1 ratio to receive the EES (Xience V, Abbott Vascular, or PROMUS (Abbott Vascular's [Abbott Park, Illinois] privately labeled XIENCE V Everolimus Eluting Coronary Stent System distributed by Boston Scientific, Natick, Massachusetts) or the SES (Cypher Select+, Cordis [Miami, Florida], Johnson & Johnson [New Brunswick, New Jersey]). An independent organization computer-generated the allocation sequence, stratified by sex and the presence of diabetes. Patients were assigned to treatment through an automated telephone allocation service. Although operators were unblinded, all individuals analyzing data were masked to treatment assignment.

STUDY PROCEDURES. EES were available in diameters of 2.25 to 4.0 mm and lengths of 8 to 28 mm. The SES were available in diameters of 2.25 to 3.5 mm and lengths of 8 to 33 mm. Stents were implanted according to standard techniques. Direct stenting without previous balloon dilation was allowed. Before or at the time of the procedure, patients received at least 75 mg of aspirin, a 600-mg loading dose of clopidogrel, and a dose of unfractionated heparin (5,000 IU or 70 to 100 IU/kg). Glycoprotein IIb/IIIa inhibitors were used at the operator's discretion. Recommended post-procedure dual-antiplatelet regimens were aspirin 75 mg/day for life and clopidogrel 75 mg/day for 1 year.

ABBREVIATIONS AND ACRONYMS

- CI** = confidence interval
- DES** = drug-eluting stent(s)
- EES** = everolimus-eluting stent(s)
- HR** = hazard ratio
- MI** = myocardial infarction
- PES** = paclitaxel-eluting stent(s)
- SES** = sirolimus-eluting stent(s)
- TLR** = target lesion revascularization
- TVR** = target vessel revascularization
- ZES** = zotarolimus-eluting stent(s)

	Everolimus-Eluting Stent (n = 1,390)	Sirolimus-Eluting Stent (n = 1,384)	p Value
Age, yrs	64.2 ± 10.9	64.0 ± 10.8	0.68
Men	1,055 (75.9)	1,041 (75.2)	0.68
Diabetes mellitus	194/1,390 (14.0)	196/1,384 (14.2)	0.88
Arterial hypertension	689/1,215 (56.7)	649/1,207 (53.8)	0.15
Hypercholesterolemia	866/1,218 (71.1)	859/1,208 (71.1)	1.00
Current smoker	344/1,178 (29.2)	353/1,162 (30.4)	0.53
Body mass index, kg/m ²	27.5 ± 4.7	27.4 ± 4.4	0.43
Previous myocardial infarction	276/1,223 (22.6)	259/1,214 (21.3)	0.46
Previous percutaneous coronary intervention	264/1,227 (21.5)	250/1,214 (20.6)	0.58
Previous coronary artery bypass grafting	118/1,227 (9.6)	97/1,214 (8.0)	0.16
Indication for percutaneous coronary intervention			0.46
ST-segment elevation myocardial infarction	122 (8.8)	145 (10.5)	
Non-ST-segment elevation myocardial infarction or unstable angina	458 (32.9)	453 (32.7)	
Stable angina	773 (55.6)	754 (54.4)	
Other	37 (2.7)	32 (2.3)	
No. of lesions treated	1,805	1,779	
Target lesions per patient			0.85
1	1,062 (76.4)	1,072 (77.5)	
2	256 (18.4)	244 (17.6)	
3	60 (4.3)	54 (3.9)	
>3	12 (0.9)	14 (1.0)	
No. per patient	1.3 (0.6)	1.3 (0.6)	0.56
No. of stents			
Per patient	1.6 (1.0)	1.6 (0.9)	0.21
Per lesion	1.3 (0.6)	1.2 (0.6)	0.26
Total stent length (mm)			
Per patient	26.4 (17.5)	26.6 (18.2)	0.78
Per lesion	20.3 (12.3)	20.7 (12.9)	0.38

Values shown are mean ± SD, number (%), or n/N (%).

ENDPOINTS. Definitions of endpoints are provided elsewhere (12). The primary endpoint was a combination of safety (cardiac death, myocardial infarction [MI], definite stent thrombosis) and efficacy (clinically indicated target vessel revascularization [TVR]) parameters within 9 months of stent implantation. Further patient-related composite (all death, all MI, or any revascularization) and stent-related composite outcomes (cardiac death, target vessel MI, or ischemia-driven target lesion revascularization [TLR]) were assessed. Individual components of the primary endpoint comprised the secondary endpoints: cardiac death rate; MI rate; rate of clinically indicated TVR; rate of probable, possible, definite stent thrombosis rate; overall stent thrombosis according to the Academic Research Consortium definition (13); and symptom-driven TLR. The 3-year pre-specified endpoints were composites of safety and efficacy (cardiac death, MI, and TVR and definite stent thrombosis) with specific focus on very late definite stent thrombosis of the first-generation SES

Cypher Select+ and the second-generation EES Xience V/Promus stent.

Comorbidity. For all patients, we obtained data on all hospital diagnoses from the Danish National Registry of Patients covering all Danish hospitals from 1977 until the implantation date (14). We then computed Charlson Comorbidity Index score, which covers 19 major disease categories, including diabetes mellitus, heart failure, cerebrovascular diseases, and cancer (15).

CLINICAL EVENT DETECTION. Clinically driven event detection was used to avoid study-induced reinterventions. Data on mortality, hospital admission, coronary angiography, repeat percutaneous coronary intervention, and coronary artery bypass surgery were obtained for all randomly allocated patients from the following national Danish administrative and healthcare registries: the Civil Registration System; the Western Denmark Heart Registry (16); the Danish National Registry of Patients (14), which maintains records on all hospitalizations in

Denmark. An independent event committee, masked to treatment group assignment during the adjudication process, reviewed all endpoints and source documents to adjudicate causes of death, reasons for hospital admission, and diagnosis of MI. Two dedicated percutaneous coronary intervention operators at each participating center reviewed cine films for the event committee to classify stent thrombosis and TVR (with either percutaneous coronary intervention or coronary artery bypass grafting). The Danish National Health Service provides universal tax-supported health care, guaranteeing residents free access to general practitioners and hospitals. The Danish Civil Registration System has kept electronic records on sex, birth date, residence, emigration date, and vital status changes since 1968 (17), with daily updates; the 10-digit civil registration number assigned at birth and used in all registries allows accurate record linkage. The Civil Registration System provided vital status data for our study participants and minimized loss to follow-up. The National Registry of Causes of Deaths and the Danish National Registry of Patients provided information on causes of death and diagnoses assigned by the treating physician during hospitalizations (coded according to the International Classification of Diseases, 10th Revision) (14).

STATISTICAL ANALYSIS. The trial was powered for assessing noninferiority of the EES to the sirolimus-eluting stent (SES) with respect to the primary endpoint at 9 months. The sample of size 1,339 assumes a 0% lost-to-follow-up rate given the use of the Civil Registration System. For the present study, we performed 2-sided 95% confidence intervals (CI) and 2-sided p values for superiority for all endpoints. Distributions of continuous variables were compared between study groups using the 2-sample *t* test (or Cochran test for cases of unequal variance) or the Mann-Whitney *U* test, depending on whether the data followed a normal distribution. Distributions of categorical variables were compared using the chi-square test. In analyses of every endpoint, follow-up continued until the date of an endpoint event, death, emigration, or 36 months after stent implantation, whichever came first. Cumulative incidence functions were computed taking into account death as a competing risk (18). We used Cox regression to determine the subhazard ratios by keeping death in the risk set until the potential censoring time after 3 years. Patients treated with the SES were used as the reference group for overall and subgroup analyses. Hazard ratios (HRs) were calculated for major adverse cardiac events at 36-month follow-up for

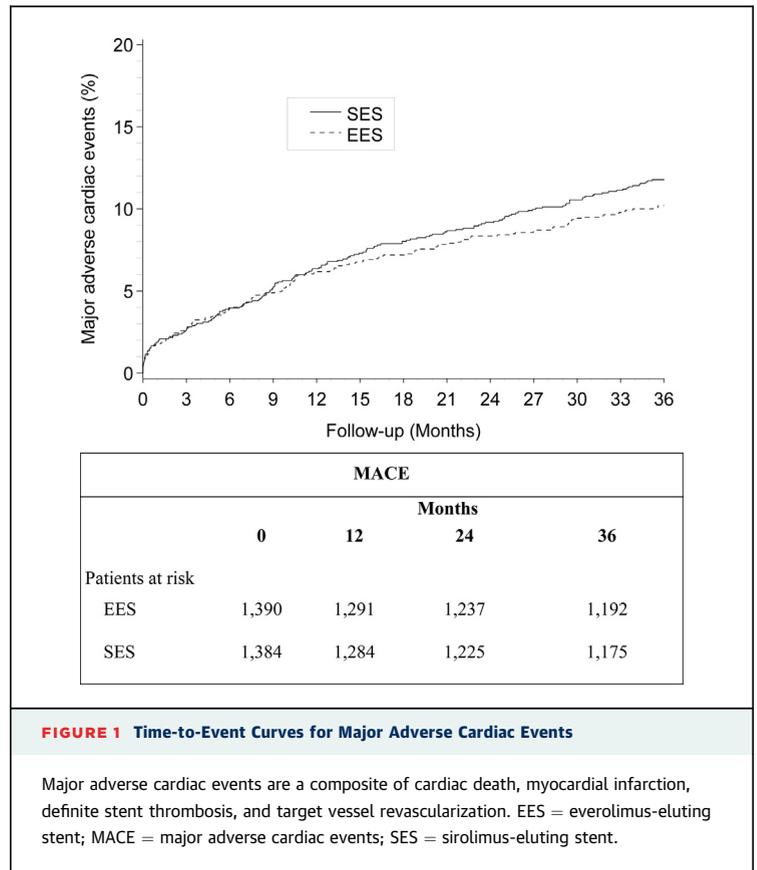


FIGURE 1 Time-to-Event Curves for Major Adverse Cardiac Events

Major adverse cardiac events are a composite of cardiac death, myocardial infarction, definite stent thrombosis, and target vessel revascularization. EES = everolimus-eluting stent; MACE = major adverse cardiac events; SES = sirolimus-eluting stent.

pre-specified patient subgroups (based on baseline demographic and clinical characteristics). The intention-to-treat principle was used in all analyses. A 2-sided p value < 0.05 was considered to indicate statistical significance. Analyses were conducted using SAS software version 9.2 (SAS Institute, Cary, North Carolina). This trial is registered with ClinicalTrials.gov (NCT00552877).

RESULTS

A total of 2,774 patients with 3,584 lesions were randomly assigned to receive either the EES (1,390 patients with 1,805 lesions) or the SES (1,384 patients with 1,779 lesions). Four patients were lost to follow-up (on days 187, 637, and 675) because of emigration (these persons were considered a success (nonevent) for the primary endpoint analysis). Complete follow-up data were available for 2,770 patients (99.9%). Baseline patient characteristics are summarized in **Table 1**. Lesion and procedure characteristics did not differ significantly between the 2 stent groups except for the maximal pressure during stent implantation, which was higher in the SES group (16.6 ± 4.2 atm vs. 17.4 ± 4.2 atm; p < 0.001) (12).

TABLE 2 Clinical Outcomes				
	EES Patients (n = 1,390)	SES Patients (n = 1,384)	HR* (95% CI)	p Value†
Events at 3 years				
Patient-related outcome	251 (18.1)	268 (19.4)	0.92 (0.78-1.10)	0.37
Stent-related outcome	93 (6.7)	105 (7.6)	0.88 (0.67-1.17)	0.38
Composite endpoint‡	142 (10.2)	163 (11.8)	0.86 (0.69-1.08)	0.20
Death				
All-cause mortality	100 (7.2)	93 (6.7)	1.07 (0.81-1.42)	0.62
Cardiac	44 (3.2)	42 (3.0)	1.05 (0.69-1.60)	0.84
Noncardiac	56 (4.0)	51 (3.7)	1.10 (0.75-1.60)	0.63
Myocardial infarction				
Target vessel related	31 (2.2)	46 (3.3)	0.67 (0.42-1.05)	0.08
Target vessel related	16 (1.2)	26 (1.9)	0.61 (0.33-1.14)	0.12
Nontarget vessel related	15 (1.1)	20 (1.5)	0.74 (0.38-1.45)	0.39
Stent thrombosis§				
Definite	3 (0.2)	20 (1.4)	0.15 (0.04-0.50)	0.002
Acute (<24 h)	0 (0.0)	3 (0.2)	–	–
Subacute (24 h–30 days)	2 (0.1)	4 (0.3)	0.50 (0.09-2.71)	0.42
Late (>30 days to 12 mo)	0 (0.0)	2 (0.1)	–	–
Very late (>12 mo)	1 (0.1)	11 (0.8)	0.09 (0.01-0.70)	0.021
Probable	7 (0.5)	4 (0.3)	1.74 (0.51-5.96)	0.38
Definite or probable	10 (0.7)	24 (1.7)	0.41 (0.20-0.87)	0.019
Possible	15 (1.1)	9 (0.7)	1.67 (0.73-3.81)	0.23
Definite, probable, or possible	25 (1.8)	33 (2.4)	0.75 (0.45-1.27)	0.28
Target vessel revascularization	91 (6.5)	110 (7.9)	0.82 (0.62-1.09)	0.16
Target lesion revascularization	50 (3.6)	66 (4.8)	0.75 (0.52-1.04)	0.13
Target lesion revascularization (patients censored at the time of stent thrombosis)	48 (3.5)	46 (3.3)	1.03 (0.69-1.55)	0.87
Nontarget vessel revascularization	98 (7.1)	112 (8.1)	0.86 (0.66-1.13)	0.28
Any revascularization	153 (11.0)	183 (13.2)	0.82 (0.66-1.02)	0.07
Values shown are number (%) unless otherwise indicated. *From a Cox regression model. †Two-sided from a Cox regression model. ‡Primary endpoint. Composite of major adverse cardiac events: cardiac death, myocardial infarction, definite stent thrombosis, and clinically-driven target vessel revascularization. Patient-related outcome: all death, all myocardial infarctions, or any revascularization. Stent-related outcome: cardiac death, target vessel myocardial infarction, or ischemia-driven target lesion revascularization. §Academic Research Consortium definition.				
CI = confidence interval; EES = everolimus-eluting stent; HR = hazard ratio; SES = sirolimus-eluting stent.				

At 3 years, the composite endpoint MACE occurred in 142 patients (10.2%) in the EES group and in 163 patients (11.8%) in the SES group (HR: 0.86, 95% CI: 0.69 to 1.08) (Fig. 1 and Table 2). The patient-related outcome (all death, all MI, or any revascularization): 251 (18.1%) patients treated with the EES versus 268 (19.4%) patients treated with the SES, (HR; 0.92, 95% CI: 0.78 to 1.10), and the stent-related outcome (cardiac death, target vessel MI, or ischemia-driven TLR): 93 (6.7%) patients treated with the EES versus 105 (7.6%) patients treated with the SES (HR: 0.88, 95% CI: 0.67 to 1.17) did not differ between groups (Table 2).

The 3-year rate of definite stent thrombosis was lower in the EES group (3 patients [0.2%] vs. 20 [1.4%] patients; HR: 0.15, 95% CI: 0.04 to 0.50) (Fig. 2 and Table 2). Late definite stent thrombosis was not seen in the EES group compared with 2 (0.1%) in the SES group, and very late definite stent thrombosis was significantly lower in the EES group compared with the SES group 1 (0.1% vs. 11 (0.8%); HR: 0.09, 95% CI:

0.01 to 0.70). Patients with very late definite stent thrombosis were all on monotherapy with aspirin, whereas the dual-antiplatelet therapy status for the patients without MACE was unknown. Overall definite/probable stent thrombosis rates were significantly lower with EES (10 [0.7%]) compared with SES (24 [1.7%]) (HR: 0.41, 95% CI: 0.20 to 0.87).

Clinically driven TLR was performed in 50 patients (3.6%) in the EES group and in 66 patients (4.8%) in the SES group (HR: 0.75, 95% CI: 0.52 to 1.04) (Fig. 2 and Table 2). Assessing TLR after censoring the patient at the time of the stent thrombosis (before TLR), the TLR rate did not differ significantly between the 2 groups: EES group, 3.5% vs. SES group, 3.3% (HR: 1.03, 95% CI: 0.69 to 1.55). Findings for the combined endpoint MACE were consistent across pre-specified stratified analyses (Fig. 3). The main endpoints (cardiac death, MI, TVR) are presented separately for the first year and a separate landmark analysis from 1 to 3 years in Table 3.

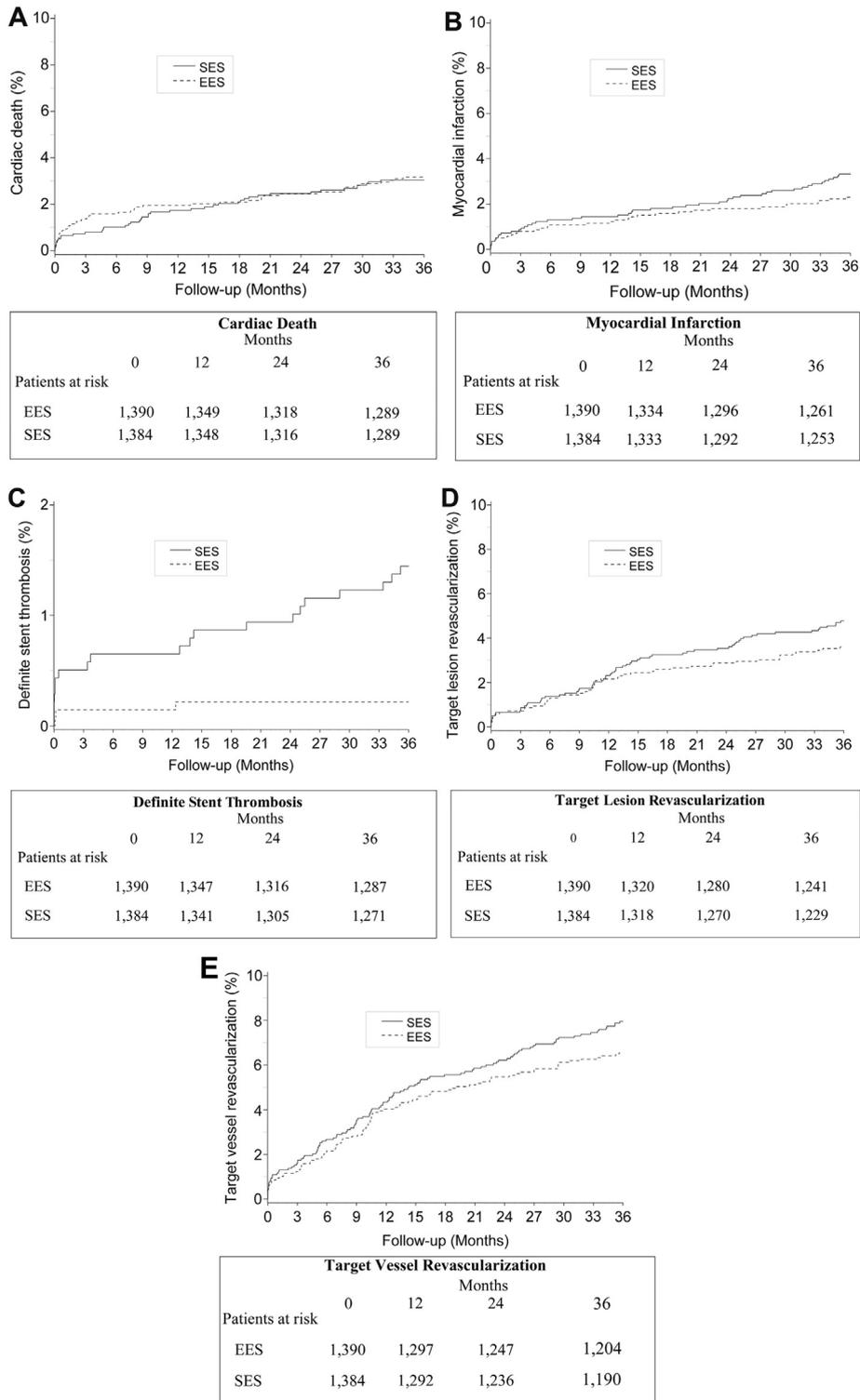


FIGURE 2 Time-to-Event Curves for Cardiac Death, Myocardial Infarction, Definite Stent Thrombosis, Target Lesion Revascularization and Target Vessel Revascularization

(A) Cardiac death, (B) myocardial infarction, (C) definite stent thrombosis, (D) target lesion revascularization, and (E) target vessel revascularization. Abbreviations as in Table 1.

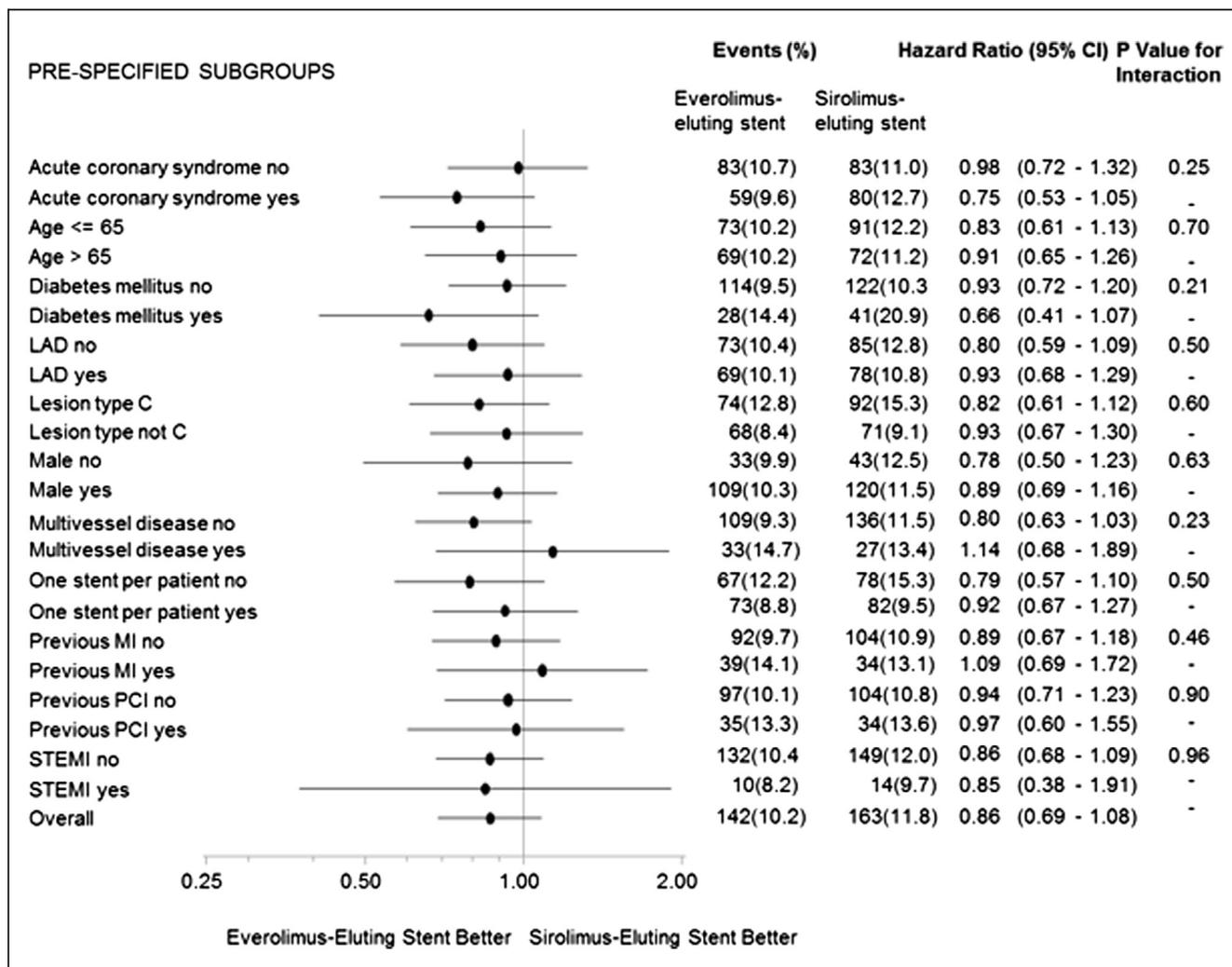


FIGURE 3 Prespecified Subgroup Analysis for the Primary Endpoint at 3-Year Follow-up

Data are presented by number of patients. Major adverse cardiac events are a composite of cardiac death, myocardial infarction, definite stent thrombosis, and target vessel revascularization. CI = confidence interval; HR = hazard ratio; LAD = left anterior descending artery; MI = myocardial infarction; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction.

DISCUSSION

The SORT OUT IV trial provides long-term head-to-head randomized comparison of the EES and the SES. At 9-month follow-up, we documented non-inferiority of the EES versus the SES. Furthermore, both overall and across a variety of patient and lesion subgroups, the 2 DES yielded similar composite endpoint results (12). The present data show that this result was maintained at 3-year follow-up for the composite MACE endpoint, the composite lesion-related endpoint, and the composite patient-related endpoint (all death, all MI, or any revascularization). Of note, however, EES was associated

with lower rates of definite stent thrombosis, which was largely attributable to a significant lower risk of very late definite stent thrombosis.

The favorable stent thrombosis rate for the second-generation DES has awaited confirmation in longer term follow-up randomized studies. In the LEADERS (Biolimus-Eluting Stent With Biodegradable Polymer Versus Sirolimus-Eluting Stent With Durable Polymer for Coronary Revascularisation) (19) and the COMPARE (6), an increasing divergence in outcomes between early-generation SES or PES and the newer generation biolimus-eluting stent or the EES was found in favor of the newer generation stent. This is in accordance with the result of the SORT OUT IV with

extended long-term follow-up to 3 years where the composite endpoint safety except cardiac death and efficacy components were numerically lower in the EES-treated group compared with the SES group. The rate of definite stent thrombosis and very late definite stent thrombosis was significantly lower in the EES-treated group; however, as this event occurs in a small number of patients, it may not influence the other endpoint components unless longer follow-up is performed. Data from the Western Denmark Heart Registry has shown that the occurrence of stent thrombosis was associated with an increased mortality risk in the following 2 years after the stent thrombosis (HR: 2.71, 95% CI: 1.72 to 4.27) compared with cases without stent thrombosis (20). In the present study, a general lack of statistical power due to an overall low number of definite stent thromboses may be an explanation for stent thrombosis not influencing mortality. In the ISAR-TEST-4 (Intracoronary Stenting and Angiographic Results: Test Efficacy of 3 Limus-Eluting Stents) trial (21), which compared EES with SES, clinical events continued to accrue at a low rate out to 3 years in both groups, and no significant difference between the EES and SES groups with regard to the primary endpoint was observed. Moreover, the rate of definite/probable stent thrombosis did not differ significantly between the 2 groups (1.4% vs. 1.9%). A registry study comparing the long-term performance of EES and SES by propensity-score matching found that definite stent thrombosis was less frequent among patients treated with EES (22). Meta-analyses have shown that the thin-strut EES may be associated with lower rates of definite ST than other DES, and, unexpectedly, even lower than bare metal stents (23). The notion of a DES being safer than a BMS represents a paradigm shift in the evolution of percutaneous coronary intervention.

In the RESOLUTE trial (8), the EES was associated with significantly less definite stent thrombosis than the slow-release Resolute ZES after 2 years of follow-up. However, in the SORT OUT III trial, the fast-release Endeavor ZES was associated with a reduced risk of very late definite stent thrombosis compared with the SES at 3-year follow-up (9), although definite stent thrombosis had occurred more frequently in the ZES group compared with SES group within the first year after the stent implantation.

The favorable stent thrombosis rate for the EES stent has awaited confirmation in longer term follow-up randomized studies, and as the rate of definite stent thrombosis is presented as a secondary endpoint, the short-term results after 1 year have been interpreted with caution and need replication and long-term follow-up to confirm that they are not

TABLE 3 Clinical outcomes separately for the first year and a separate landmark analysis from 1-3 years

	EES Patients (n = 1,390)	SES Patients (n = 1,384)	HR* (95% CI)	p Value†
Events at 0-12 mo				
Composite endpoint‡	85 (6.1)	88 (6.4)	0.96 (0.71-1.29)	0.79
Death	41 (2.9)	35 (2.5)	1.17 (0.75-1.84)	0.49
Cardiac death	27 (1.9)	24 (1.7)	1.12 (0.65-1.95)	0.68
Myocardial infarction	16 (1.2)	20 (1.4)	0.80 (0.41-1.54)	0.50
Target vessel revascularization	56 (4.0)	60 (4.3)	0.93 (0.64-1.33)	0.68
Target lesion revascularization	30 (2.2)	32 (2.3)	0.93 (0.57-1.53)	0.78
Events at 12-36 mo				
Composite endpoint‡	57 (4.4)	75 (5.8)	0.75 (0.53-1.06)	0.10
Death	59 (4.4)	58 (4.3)	1.02 (0.71-1.46)	0.93
Cardiac death	17 (1.3)	18 (1.3)	0.94 (0.49-1.83)	0.86
Myocardial infarction	15 (1.1)	26 (1.9)	0.57 (0.30-1.08)	0.08
Target vessel revascularization	35 (2.6)	50 (3.8)	0.69 (0.45-1.06)	0.09
Target lesion revascularization	20 (1.5)	34 (2.5)	0.58 (0.33-1.01)	0.05

*From a Cox regression model. †Two-sided from a Cox regression model. ‡Primary endpoint. Composite of major adverse cardiac events: cardiac death, myocardial infarction, definite stent thrombosis, and clinically driven target vessel revascularization. Abbreviations as in Table 2.

spurious. Combined, the results with long-term follow-up confirm that the second-generation EES have a better long-term safety profile compared with the first-generation SES and PES. Further, the importance of long-term follow-up in randomized studies comparing DES is highlighted.

Like most stent trials, the SORT OUT IV trial was designed as a single-blind study, and we believe that the lack of double-blinding would not influence the results as all endpoints were objective and determined by an event committee who was blinded to treatment group assignment during the adjudication process. Therefore, we expect that the event rate in our study is representative of the real event rate among this patient population.

CONCLUSIONS

MACE rates did not differ significantly between EES- and SES-treated patients at 3-year follow-up. A significant reduction of overall and very late definite stent thrombosis was found in the EES group.

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REFERENCES

1. Morice MC, Serruys PW, Sousa JE, et al. A randomized comparison of a sirolimus-eluting stent with a standard stent for coronary revascularization. *N Engl J Med* 2002;346:1773-80.
2. Moses JW, Leon MB, Popma JJ, et al. Sirolimus-eluting stents versus standard stents in patients with stenosis in a native coronary artery. *N Engl J Med* 2003;349:1315-23.
3. Stone GW, Ellis SG, Cox DA, et al. A polymer-based, paclitaxel-eluting stent in patients with coronary artery disease. *N Engl J Med* 2004;350:221-31.
4. Daemen J, Wenaweser P, Tsuchida K, et al. Early and late coronary stent thrombosis of sirolimus-eluting and paclitaxel-eluting stents in routine clinical practice: data from a large two-institutional cohort study. *Lancet* 2007;369:667-78.
5. Jensen LO, Tilsted HH, Thayssen P, et al. Paclitaxel and sirolimus eluting stents versus bare metal stents: long-term risk of stent thrombosis and other outcomes. From the Western Denmark Heart Registry. *EuroIntervention* 2010;5:898-905.
6. Smits PC, Kedhi E, Royaards KJ, et al. 2-year follow-up of a randomized controlled trial of everolimus- and paclitaxel-eluting stents for coronary revascularization in daily practice. COMPARE (Comparison of the everolimus eluting XIENCE-V stent with the paclitaxel eluting TAXUS LIBERTE stent in all-comers: a randomized open label trial). *J Am Coll Cardiol* 2011;58:11-8.
7. Stone GW, Rizvi A, Sudhir K, et al. Randomized comparison of everolimus- and paclitaxel-eluting stents. 2-year follow-up from the SPIRIT (Clinical Evaluation of the XIENCE V Everolimus Eluting Coronary Stent System) IV trial. *J Am Coll Cardiol* 2011;58:19-25.
8. Silber S, Windecker S, Vranckx P, Serruys PW. Unrestricted randomised use of two new generation drug-eluting coronary stents: 2-year patient-related versus stent-related outcomes from the RESOLUTE All Comers trial. *Lancet* 2011;377:1241-7.
9. Maeng M, Tilsted HH, Jensen LO, et al. 3-Year clinical outcomes in the randomized SORT OUT III superiority trial comparing zotarolimus- and sirolimus-eluting coronary stents. *J Am Coll Cardiol Intv* 2012;5:812-8.
10. Kirtane AJ, Leon MB, Ball MW, et al. The "final" 5-year follow-up from the ENDEAVOR IV trial comparing a zotarolimus-eluting stent with a paclitaxel-eluting stent. *J Am Coll Cardiol Intv* 2013;6:325-33.
11. Jensen LO, Thayssen P, Tilsted HH, et al. Rationale and design of a randomized clinical comparison of everolimus-eluting (Xience V/Pro-mus) and sirolimus-eluting (cypher select+) coronary stents in unselected patients with coronary heart disease. *Cardiology* 2010;116:73-8.
12. Jensen LO, Thayssen P, Hansen HS, et al. Randomized comparison of everolimus-eluting and sirolimus-eluting stents in patients treated with percutaneous coronary intervention. The SORT OUT IV Trial. *Circulation* 2012;125:1246-55.
13. Cutlip DE, Windecker S, Mehran R, et al. Clinical end points in coronary stent trials: a case for standardized definitions. *Circulation* 2007;115:2344-51.
14. Andersen TF, Madsen M, Jorgensen J, Mellemkjoer L, Olsen JH. The Danish National Hospital Register. A valuable source of data for modern health sciences. *Dan Med Bull* 1999;46:263-8.
15. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987;40:373-83.
16. Jensen LO, Maeng M, Kaltoft A, et al. Stent thrombosis, myocardial infarction, and death after drug-eluting and bare-metal stent coronary interventions. *J Am Coll Cardiol* 2007;50:463-70.
17. Frank L. Epidemiology. When an entire country is a cohort. *Science* 2000;287:2398-9.
18. Gooley TA, Leisenring W, Crowley J, Storer BE. Estimation of failure probabilities in the presence of competing risks: new representations of old estimators. *Stat Med* 1999;18:695-706.
19. Stefanini GG, Kalesan B, Serruys PW, et al. Long-term clinical outcomes of biodegradable polymer biolimus-eluting stents versus durable polymer sirolimus-eluting stents in patients with coronary artery disease (LEADERS): 4 year follow-up of a randomised non-inferiority trial. *Lancet* 2011;378:1940-8.
20. Thayssen P, Jensen LO, Lassen JF, et al. The risk and prognostic impact of definite stent thrombosis or in-stent restenosis after coronary stent implantation. *EuroIntervention* 2012;8:591-8.
21. Byrne RA, Kastrati A, Massberg S, et al. Biodegradable polymer versus permanent polymer drug-eluting stents and everolimus- versus sirolimus-eluting stents in patients with coronary artery disease: 3-year outcomes from a randomized clinical trial. *J Am Coll Cardiol* 2011;58:1325-31.
22. Raber L, Juni P, Nuesch E, et al. Long-term comparison of everolimus-eluting and sirolimus-eluting stents for coronary revascularization. *J Am Coll Cardiol* 2011;57:2143-51.
23. Palmerini T, Biondi-Zoccai G, Della RD, et al. Stent thrombosis with drug-eluting and bare-metal stents: evidence from a comprehensive network meta-analysis. *Lancet* 2012;379:1393-402.

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